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Chapter 1

The medical and cultural history of testosterone and the testes

Eberhard Nieschlag and Susan Nieschlag

1.1 Introduction

Although the term "hormone" was coined only as late as 1905 (Starling 1905; Henderson 2005), the biological effects of hormones were known for much longer and probably from the early beginnings of humankind. The over- or underproduction of hormones as the fundamental pathophysiological principle in endocrine disorders often produces phenotypical alterations that can be easily recognized. Similarly, elimination of hormones by removing the respective gland or replacing the hormones in a deficient organism is a basic tool of experimental endocrinology. In their exposed scrotal position, the testes are easily accessible for manipulation, be it by accidental or by inflicted trauma. The causal relationship between absence of the glands and the resulting biological effects – before or after puberty – is easily recognizable, and that is why effects of testosterone, or rather its absence, have been known from early on. Victor C. Medvei (1993), the master of the history of endocrinology, summarized this phenomenon by saying "The oldest key to the endocrine treasure trove: the testicles."

Indeed the lack of functional effects of the testes has been noted since antiquity and, in the light of modern science, these observations are often entertaining for today's reader, but at the same time they are also educational for the medical scholar. In addition, they reflect the socio-cultural environment of the time when they were observed or exploited, so that the history of testosterone and the testes is not only of medical interest, but also of interest to the general public.

The authors of this chapter are not trained historians, but the first author has a keen interest in the history of medicine, as documented early by his first medical publication dealing with the biography of Otto Deiters (1834–1863), the describer of the Deiters' cells and nucleus (Nieschlag 1965). While specializing in endocrinology and andrology, historical events surrounding testosterone were collected along with the scientific studies, culminating in the request by the Royal College of Physicians (London) in 2005 to commemorate the hundredth anniversary of the term "hormone" by a talk on "The history of testosterone," thus precipitating more systematic research on the subject. Since then a more complete but still patchy picture has been developed, which is presented here. As it is impossible to give a full history of

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testosterone and the testes here, and many developments occurred simultaneously in various epochs, the material is summarized under three more or less systematic subheadings as follows (1.2–1.4). Nevertheless, this is not a systematic review, but rather a collection of historical highlights.

1.2 From antiquity to the age of enlightenment

1.2.1 Ancient Egypt

One of the oldest hypogonadal patients whose image has been preserved appears to be Vizier Hemiunu, the architect of the pyramid of Giza. The statue in his mausoleum dating from 2531 BC (Roemer-Pelizaeus Museum, Hildesheim) shows a seated man with straight hairline, no beard, bilateral gynecomastia and myxedematous lower legs. In contrast, other statues from that period show well-built athletic men; for instance the statue of Amenemhat II (1919–1884 BC) (which travelled in 2011 from the Egyptian Museum in Berlin to be exhibited in the Metropolitan Museum in New York). The plaque on Hemiunu's statue describes his achievements as an architect, but does not mention a wife or children as was customary at the time, indicating that he may have been infertile. He could have suffered from hypopituitarism including hypogonadism, perhaps caused by a prolactinoma, but Klinefelter syndrome would also be a possible diagnosis.

1.2.2 Greco-Roman period

Aristotle (384–322 BC), the universal genius and philosopher of the Hellenistic era, observed and wrote on *The Generation of Animals*, in which he described the generation of visible organs in fertilized chicken eggs. He knew the effects of castration in men as well as in animals, and described its consequences for animal husbandry. For humans, he developed the fascinating hypothesis that the right testis produces boys and the left testis girls. This could be based on case reports of men with unilateral anorchia or traumatic loss of one testis. To date no study could be traced verifying or falsifying this hypothesis, and a proposed controlled clinical study to be performed today would most likely not be met by agreement of an ethics committee. This also demonstrates how misleading case reports may be.

Aristotle also developed a theory of fertilization: semen is the activating agonist of the "soul" fertilizing the passive female soil. Like his other work, this theory had a long-lasting effect on science and was only superseded by Leeuwenhoek and Spallanzani about 2000 years later (see below).

Also dating from the Hellenistic time (about 300 BC) until the first century AD, the fertility cult around Diana/Artemis Ephesina was popular in the entire Greco-Roman world, and was especially promoted by the emperors Trajan (53–117) and Hadrian (76–138). This cult had its origin in the temple of Artemis in Ephesos, the Artemision, where the "magna mater" was worshipped. The statues, of which an excellent example can be seen in the National Archaeological Museum in Naples, are characterized by multiple oval objects fixed to the goddess's frontal thorax. Until quite recently these were interpreted as breasts, but were in reality bull or ram testes whose bearers were sacrificed to the goddess, following which their testes were fixed to the originally wooden statue, then emanating fertility and potency to the worshipper. This cult is thus based on knowledge of the powers of generation connected with the testes.

1.2.3 Castration through the times

In Greek mythology castration already occurred among the first generation of gods. Gaea, mother earth, grew out of the chaos and produced Uranos by parthenogenesis, with whom she then generated the titan Chronos. When Uranos prevented Gaea from creating children with their son Chronos, she induced Chronos to castrate his father. This episode has been depicted beautifully in a fresco by Giorgio Vasari (1511–1574) in the Palazzo Vecchio in Florence. Uranos' testes, thrown into the sea, caused the water to foam, and out of these bubbles the foam-born goddess of love Aphrodite (= Venus) was born. Quite extraordinary events in terms of reproductive physiology!

In the real world, castration has been practiced for socio-cultural purposes since antiquity. Its major purpose was to generate obedient slaves who were loyal to their masters or rulers and who, being infertile, could not create competing offspring. Set to guarding harems, they also, and in larger numbers, obtained influential administrative and political positions as in China, and formed elite troops (Mitamura 1992; Flaig 2009).

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Although most likely already practiced earlier, the earliest documentation of creating eunuchs in China dates back to about 1300 BC. The Chinese eunuch system, with several thousands at a time, continued until the end of the imperial system in 1912. In the nineteenth century there were still about 2000 eunuchs at the imperial court in Beijing. The last Chinese eunuch died at the age of 93 in 1996. Only the fact that imperial eunuchs could obtain high-ranking positions and considerable power as well as wealth makes it plausible that adult men underwent this gruesome operation. It was performed by "licensed surgeons" just outside the imperial court in Beijing, by cutting off testes *and* penis. About 25% of the volunteers did not survive this bloody operation. The severed genitals were kept in a box, as shown in the film "The Last Emperor" (1987), and were eventually buried with their owner.

Eunuchs probably already existed in ancient Egypt. From the times of the legendary Queen Semiramis (about 800 BC) eunuchs were reported from Assyria, and the system developed and continued into the Islamic world in the Middle East and North Africa. Over centuries, slaves were deported from Sub-Saharan Africa to the Islamic cities and courts, and many of the slaves who survived the exhausting march through the desert were then castrated to serve as laborers, guards, administrators and even soldiers (Barth 1857). It is astonishing that these tasks could be fulfilled without the anabolic effects of testosterone.

It has been estimated that the transatlantic deportation of Africans to the Americas between 1450 and 1870 comprised about 11.5 million people, while the entire Islamic deportation of slaves from Africa between 650 and 1920 amounted to 17 million people, and several million of these African slaves were castrated. This constant drain of manpower effectively prevented economic and cultural development of Sub-Saharan Africa. In medieval times slaves were also exported from Europe to the Islamic countries. These slaves were mainly from Eastern European (Slavic) and Central Asian countries. There were well-established slave routes through Europe, and Verdun has the questionable historical fame of having been the European center for castration of slaves on their way from the East to the South at those times (Flaig 2009).

Castration has also been practiced as lawful punishment. In medieval Scandinavia, castration combined with blinding was administered for high treason, especially when the insurgent was a close relative whom one did not want to kill directly. As told in the Islendinga Saga, Sturla of the Sturlungar Clan in Iceland castrated and blinded his rebelling relative Oraekja Snorrason in 1236 (personal communication from U. Ebel, Chair of Scandinavian Sciences, University of Münster, 2007). When the Normans migrated south they also introduced this penal practice in the areas they invaded. When he established his reign in Britain after 1066, William the Conqueror abolished the Anglo-Saxon death penalty and replaced it by castration and blinding: "I also forbid that anyone shall be slain or hanged for any fault, but let his eyes be put out and let him be castrated" (Van Eickels 2004). As a further example, in Sicily in 1194 King William III was castrated and blinded after a rebellion against Emperor Henry VI. This episode forms the historical background for Klingsor's castration in the *Parsifal* epos (Tuchel 1998). The Toulouse Law Codex of 1296 described (and depicted) castration for high treason.

Throughout the centuries, castration was applied to beaten enemies by victorious soldiers for revenge and as a measure to eliminate the enemies without outright killing. When Italian troops invaded Ethiopia and lost the battle of Aduwa in 1896, supposedly 7000 Italian soldiers were castrated (Melicow 1977). As reported by Babtschenko (2007), this still happened on both sides during the Chechen War in the Caucasus in 1996.

Castration has also been reported as self-mutilation for religious reasons since ancient times in order to make a life of chastity easier. The early church father Origines (186–254) is one of the most prominent examples. In the eleventh to fourteenth centuries the sect of the Catharers, with their strongholds in Southern France, promulgated self-castration as part of a "pure" life. More recently, castration was practiced in Southern Russia among members of the Scoptic sect founded in the eighteenth century, and the medical consequences were documented (Wilson and Roehrborn 1999). The largest contemporary group of castrates are the hijras in India. They function as professional well-wishers at birth rites, and receive considerable financial rewards. Several thousand of them exist.

Castration has also been used as revenge for seduction and adultery through the centuries. For example, Paris has been reported to have castrated

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Peritanos after he had seduced his famous wife Helena (Lehrs 1832). The case of the great medieval theologian and philosopher Peter Abaelard (1079–1142) has been celebrated in history and literature. As master of the cathedral school in Paris he seduced one of his disciples, Heloise (1100–1164), whose uncle then had Abaelard castrated by paid criminals. Despite the lack of testosterone, one of the most romantic love stories documented by literature developed (Podlech 1990). This type of revenge continues into most recent times as demonstrated by an incident in Germany in 2011 when the father of a 17-year-old girl castrated her 57-year-old lover (Holzhaider 2011). These people had migrated to Germany from Kazakhstan and might have brought rules of self-justice with them.

Castration before puberty maintains the high voice of boys, so that soprano and alto voices with the acoustic volume of an adult male result. Such high-pitched voices were considered desirable among music lovers, especially at times when women were not allowed to sing in church or in operatic performances. Prepubertal castrates belonged to casts of operas in the seventeenth and eighteenth centuries; in the Vatican choirs these voices could be heard until the early twentieth century. Some of these castrates became famous soloists, such as Carlo Farinelli (1705–1782) or Domenico Annibaldi (1705–1779) (Melicow 1983; Ortkemper 1993; Jenkins 1998). The middle Italian city of Nurcia was a center for the operation on young boys. However, most of the thousands of prepubertal castrates lost their virility in vain as they did not achieve the promised career as a singer, developed only mediocre voices and were ridiculed by their contemporaries. An impression of the castrato voice, although of very low recording quality, is preserved from the last Vatican castrato, Alessandro Moreschi (1858–1922), in one of the earliest gramophone recordings, made in 1902 (available today on CD). Today countertenors applying a trained falsetto sing the castrato roles in, for example, Händel operas, but their head voices probably only approximate those of seventeenth-century castrati. Another impression of the enormous artistic talents of the castrati is provided by the recordings of the mezzo-soprano Cecilia Bartoli, who trained her voice to sing the extremely demanding arias by Nicola Porpora (1686–1768), Georg Friedrich Händel (1685–1759) and others (Bartoli 2009).

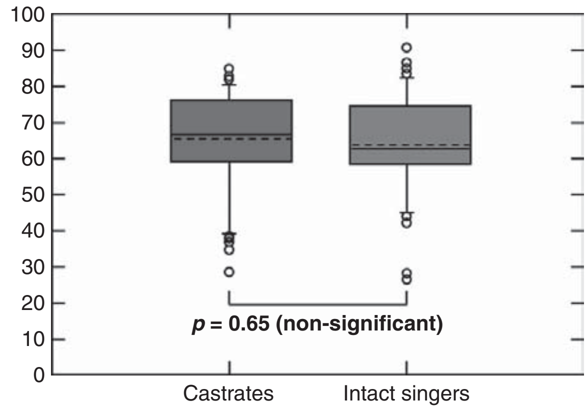

Fig. 1.1 Longevity of intact and castrated singers ($n = 50$ in each group) born between 1580 and 1859 (matched pairs of intact and castrated singers with similar birth dates were formed). (Box and whisker plots: solid line = median; broken line = mean value) (Nieschlag *et al.* 1993).

Prepubertal castration provides an involuntary experiment on the influence of testosterone on longevity. A retrospective comparison of the life expectancy of singers born between 1580 and 1859 and castrated before puberty, in order to preserve their high voices, against intact singers born at the same time, did not reveal a significant difference between the lifespan of intact and castrated singers (Fig.1.1; Nieschlag *et al.* 1993). This would imply that the presence or absence of normal male testosterone levels has no influence on life expectancy.

1.2.4 Power through polyorchidism

While removal of the testes was used to punish or to weaken the enemy or to obtain specific effects as a consequence of the lack of testosterone, a supernumerary testis was always considered a sign of extraordinary virility and sexual vigor. Several such cases have been reported anecdotally. The Venetian Condottiero Bartolomeo Colleoni (1400–1475), whose success on the battlefield as well as in the bedroom was legion (Frigeni–Careddu 1996), advertised his physical abnormality by showing three testes in his coat of arms ("*Colleoni*" in Italian means "testes"; nowadays spelled "*coglioni*").

Allegedly, in 1539 Philipp Magnanimus, Count of Hesse (1504–1567), a protagonist of the Protestant reformation, was granted permission by Martin Luther to have two wives simultaneously: Christine von Sachsen (1505–1549) and Margarethe von der Saale (1522–1566), because of his three testes.

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Because at that time bigamy was forbidden upon penalty of death, Philipp got in even more trouble with the Holy Roman Emperor than his ambitions as a religious reformer had caused. A third testis had already been diagnosed in the boy, but without ultrasound, biopsy or post-mortem examination it remains unclear what these third structures in his and other famous people's scrotums were – possibly real testes or large spermatoceles? Whatever it was, this diagnosis had a tremendous impact on the person and on historical events.

1.2.5 First description of testicular morphology and sperm

The declaration of the Netherlands as an independent state during the Thirty Years War (1618–1648), and legalized at the Westphalian Peace Treaty in Münster in 1648, resulted in an enormous upswing in economy, culture and science in this country. The medical sciences also boomed, based on proper research, especially in anatomy, as shown in Rembrandt's painting "Anatomy of Dr. Tulp" (1632).

The reproductive sciences benefited from this boom as well. It was Regnier de Graaf (1641–1673) who not only described the Graafian follicle (1672), but also published a book about the anatomy of the male reproductive tract as well as the treatment of its disorders (de Graaf 1668). He produced very detailed drawings and descriptions of the male genital organs, and was the first to discover that the testes were composed of a "collection of minute vessels or tubules which confect semen; if these tubules were disentangled without being broken and tied to one another, they would far exceed 20 Dutch ells in length." Having first described this in the edible dormouse, he then went on to the human: a classical case of translational medicine. Unfortunately, de Graaf became involved in a quarrel with his contemporary, Jan Swammerdam (1637–1680), about the question of who had first described the follicles, and during that phase he died under nebulous circumstances at the young age of 32 (Setchell 1974).

A few years after Regnier de Graaf's early and mysterious death, his friend Antoni A. Leeuwenhoek (1632–1723), together with the student Johan Hamm, used his newly invented prototype of a microscope and described the "little animals of the sperm" in a letter to the Royal Society in London in 1677 (van Leeuwenhoek 1948). Considering the primitive appearance of his microscope, the details of his morphological descriptions of sperm are amazing, and it is even more amazing that 300 years later we are still quarreling about normal and abnormal sperm morphology (Kremer 1979).

But it took another century until Lazzaro Spallanzani (1729–1799), a priest and scientist in Modena, artificially inseminated frogs and dogs and demonstrated the real function of sperm (Spallanzani 1779). By using sperm that he had preserved on ice he also became the father of cryopreservation, without which modern reproductive medicine and medicine in general would be unthinkable.

He was a very systemic investigator and insisted – quite in contrast to others at the time – that experiments needed to be repeated before results could be accepted (Gaeto 1999), a principle that prevails until today.

The anatomist Franz Leydig (1821–1908) in Würzburg described the interstitial cells of the testes in 1850 (Leydig 1850). Although he did not know their function, they still carry his name (Christensen 1996). Finally in Milan, in 1865 Enrico Sertoli (1842–1910) discovered the supporting cells in the seminiferous tubules (Sertoli 1865), also carrying his name to date (Virdis 2005).

Thus, over roughly two centuries the basic morphological elements of the testes had been described, as well as the one major product of the testes, the sperm. Even the function of sperm and fertilization had been elucidated, so that the time had come to explore the basis of testicular endocrine function.

1.2.6 Proof of endocrine function

Although the endocrine function of the testes was known through their physiological and clinical effects, their nature remained completely obscure. While William Harvey (1578–1657) had discovered the role of the heart and blood circulation in 1628, in some medical schools Galen's (AD 129–216) concept of the four bodily humors prevailed well into the nineteenth century. Against this background, it is not surprising that the idea of a hormone working as a signal transduced by circulating blood took so long to be born.

John Hunter (1728–1793) is considered by some to be the father of endocrinology, as he transplanted testes in chickens. However, his outstanding

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achievement as a scientist notwithstanding, he transplanted testes in order to demonstrate the "vital principle" of living organs. As a surgeon in the Seven Years' War (1756–1763), he saw the need for transplantation of organs and limbs, and this is what stimulated his research. He never described his testis transplantations himself, but we learn about them through a scholar, Dr. W. Irvine, in a letter to Professor Th. Hamilton in Glasgow in 1771: "...Nay more, he has many hens just now into whose abdomen when young, he has put the testes of a cock just separated from his body and his testis has got blood vessels and nerves from the part of the abdomen or viscera to which it is applied..." Far from any endocrine thought, the goal was to demonstrate the survival of the transplant (Barker Jorgensen 1971).

Such thoughts were precipitated by Arnold Adolph Berthold's (1803–1861) experiments, which also concerned transplanting chicken testes. As published in 1849, he castrated four cocks: two received an ectopic transplantation of one testis, the two others remained untreated, and he observed "They crowed quite considerably, often fought among themselves and with other young roosters and showed a normal inclination to hens... Since the testes can no longer remain in connection with their original nerves after being transplanted to a strange place... it follows that the consensus in question must be affected through the productive relationship of the testes, that is to say, through their action on the blood, and then through the suitable ensuing action of the blood on the organism as a whole." (Berthold 1849). The paper describes only four animals and comprises only four pages – in contrast to the extensive style of the time – but was epochal. However, Berthold's rival at the University of Göttingen, Rudolf Wagner (1805–1864) was jealous, tried to repeat the experiments, but failed and declared them as rubbish (Wagner 1852). And as he became the full professor of physiology, his opinion prevailed. Berthold's personality did not allow him to fight for recognition of his findings (Simmer and Simmer 1961; Simmer 1980).

As blood circulation, the essential morphological elements of the testes and the biological and clinical effects of their endocrine action were known, history could have continued straight from here to the discovery of testosterone, but due to these interpersonal quarrels and other unhappy events, further developments took an oblique route.

1.3 Detours on the way to modern medicine

1.3.1 Organotherapy

As it was known that removal of the testes caused the clinically evidenced symptoms of hypogonadism, including impotence, prescribing ingestion of testes to remedy the symptoms was a medical reflex inherent in organotherapy, practiced since antiquity. Thus the Roman Gaius Plinius Secundus (AD 23–79) recommended the consumption of animal testes to treat symptoms of testosterone deficiency. Slightly more refined was the prescription of testicular extracts for the same purpose in Arabic medicine, for example by Mensue the Elder (777–837) in Baghdad. Also, in China, raw and desiccated testes were prescribed, documented at least in the twelfth century by Hsue Shu-Wei. Around the same time, Albertus Magnus (1193–1280) in Cologne, better known as a philosopher, recommended powdered hog testes, but refined his recipe by offering the powder in wine (Medvei 1993).

Since early documentation, these potions continued to be prescribed and consumed up into the twentieth century. In the 1920s Testifortan® became a financially successful drug for treatment of impotence (Hirschfeld 1927). Its main constituent was testis extracts and yohimbine, and after the war 17α-methyltestosterone was added without changing the name. Another famous preparation from the 1920s and still marketed today is Okasa® which, among other components, also contains *testis sicca* and thereby small amounts of testosterone, as we could determine in the 1970s (unpublished data). However, as the testes synthesize testosterone but do not store it, the daily production of an adult man of about 6–8 mg is contained in roughly 1 kg of (bull) testes, and even if this amount of testosterone were to be consumed, the testosterone taken orally would be inactivated by the first-pass effect in the liver (Nieschlag *et al.* 1977). Therefore, all testicular organ therapy administered orally can only be considered as a placebo medication, which, however, may not be without its own effects (Bundesärztekammer 2011). Ultimately this type of testicular organotherapy was terminated by the advent of phosphodiesterase inhibitors.

Organotherapy literally exploded at the end of the nineteenth century when Charles E. Brown-Séquard (1847–1894), who until then was a well-reputed

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scientist and member of several scientific academies, published the results of his famous self-experimentation in the Lancet (Brown-Séquard 1889). He gave himself 1-ml injections of a mixture of one part testicular vein blood, one part semen and one part juice extracted from dog or guinea-pig testes daily, and after 20 days made astonishing observations on himself: "A radical change took place in me... I had regained at least all the strength I possessed a good many years ago. I was able to make experiments for several hours. After dinner I was able to write a paper on a difficult subject. My limbs, tested with a dynamometer, gained 6 to 7 kg in strength. The jet of urine and the power of defecation became stronger."

Certainly all these were placebo effects, but the world had obviously waited for such quackery, because in no time the "extracts of animal organs by the Brown-Séquard method" were sold all over the (western) world, and factories sprung forth in Europe as well as in America, for example next to Central Park in New York (Borell 1976). There must have been a real craze for these products, and physicians concerned about the image of the young field of endocrinology started worrying. The famous neurosurgeon Harvey W. Cushing (1869–1939), and the president of the Association of the Study of Internal Secretions, E. H. Rynearson even talked about "endocri*mi*nology" in the context of this organotherapy (Hamblen 1950). This assessment of the medical scene at the time is also reflected in contemporary cartoons and comic songs from the early twentieth century. Eventually, this type of quackery stimulated science and decent pharmaceutical companies to search for real hormones.

1.3.2 Testis transplantations

However, before science succeeded in that attempt there was another sad approach to treat hypogonadism and bring about rejuvenation and treatment for all sorts of disorders: the transplantation of testes. G. Frank Lydston (1858–1923) in Chicago was one of the first to perform human testicular transplantation from donors after experimentation in animals (Lydston 1915; Schultheiss and Engel 2003). V. D. Lespinase (1913) published his experience with transplanting human testes to patients for rejuvenation, and Leo Stanley (1920) reported 20 cases of transplantation of testes from executed prisoners to other inmates who reported signs of revitalization. Later on he turned to animals as sources for his testicular grafts and reported satisfaction on the part of the patients including 13 physicians (Stanley 1923).

These surgeons had followers in many parts of the world, for example even in Iceland where, in 1929, the surgeon Jonas Sveinsson transplanted testis slices from a poor farmer in need of money to a rich Norwegian businessman who, he then claimed, satisfied his 23-year-old wife so that he even had three children with her (Sveinsson 1969). In the Soviet Union, experimentation with human testicular transplantation continued at least into the 1980s (Shumankov and Gotsiridze 1978). The only testicular transplantation resulting in fertility of the recipient was performed by Sherman J. Silber (Silber and Rodriguez-Rigau 1980) between twin brothers.

In Vienna, Eugen Steinach (1861–1944) performed vasoligation for rejuvenation (Steinach 1920), and one of his followers, Serge Voronoff (1866–1951) turned to xenotransplantation and used monkey testes to be transplanted for rejuvenation (Voronoff 1920; 1923). He first offered his surgery in Paris, but after some scandals continued his questionable operations in Algiers, where he was obviously visited by patients from all over the world. Voronoff had followers in many countries who xenotransplanted animal testes or pieces thereof to patients in need of rejuvenation, also in the USA, where this type of treatment caused great interest among the laymen and the media (e.g. Gayton 1922). As unrest among the medical profession continued to grow, in 1927 the Royal Society of Medicine (London) sent an international committee to Voronoff in Algiers, which concluded that Voronoff's claims were all poppycock (Parkes 1965). This, and the success of upcoming steroid biochemistry finally terminated this malpractice.

However, in a transformed fashion it continued as cellular therapy by injecting suspensions of fresh cells of sheep embryos including testis cells, also for rejuvenation and revitalization, well into the second half of the twentieth century (Niehans 1952; 1960).

Meanwhile, science has progressed and, in the age of cell biology, testicular transplantation continues with the aim of inducing fertility, but now uses isolated germ cells (Brinster and Zimmermann 1994; Schlatt *et al.* 2002), and fertility has indeed been restored by this method in gamma-irradiated cocks (Trefil *et al.* 2006). Whether this may become a method to treat male infertility, for example in

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Klinefelter patients (Wistuba 2010), remains to be seen, but at least it is pursued on a rational scientific basis – as far as our present knowledge goes.

1.4 Twentieth-century science and medicine

1.4.1 The rise of steroid biochemistry

Berthold's unique discovery was superseded by organotherapy, but it was not permanently forgotten: Moritz Nussbaum (1850–1915), professor of anatomy in Bonn, repeated Berthold's experiments and confirmed the results in frogs (Nussbaum 1909), as did Eugen Steinach in rats (Steinach 1910). Finally, A. Pézard confirmed Berthold's original results in cocks (Pézard 1911), and the search for the active androgenic substance in the testes began.

From observation of the cock's comb growing under the influence of transplanted testes, Moore *et al.* (1929) established the standardized capon comb's test, measuring androgenic activity in square centimeters of comb surface. This first bioassay facilitated determination of androgenic activity in body products as well as in chemical solutions. S. Loewe and H. E. Voss (1930) used the biological effects of androgens on the accessory sex organs and developed the "cytological regeneration test," which was based on regrowth of the seminal vesicle epithelium under androgenic substances (Loewe–Voss test). The then still hypothetical male hormone was called "androkinin."

Simultaneously, steroid biochemistry emerged and the great breakthroughs were the discovery of the ring structure of steroids and bile acids at the National Institute of Medical Research in London (Rosenheim and King 1932) and at the Bavarian Academy of Sciences in Munich (Wieland and Dane 1932). A heated discussion started about whether there were three or four rings in the steroid structure and, if four rings, whether the fourth had five or six carbon atoms. Under the sponsorship of the Health Organization of the League of Nations (the predecessor of the World Health Organization, WHO), famous chemists including Edmund A. Doisy, Adolf Butenandt and Guy Marrian assembled at University College London and reached the consensus that steroids had four rings, and the fourth ring had five carbon atoms (Butenandt 1980). Shortly before, these eminent researchers, including Ernest Laqueur, had isolated pregnanediol and estrone from pregnant mare urine provided by various drug companies cooperating with scientists in order to replace the miscredited organotherapy and to bring proper hormone substitution to patients (see Table 1.1) (Simmer 1982).

1.4.2 Testosterone is born

In 1931 Butenandt isolated the androgenic steroid, androsterone (androstan-3α-ol-17-one), from urine, for which he required 15 000 liters provided by young

Table 1.1 Early isolation of reproductive steroids (for references see the text)

1928 Pregnanediol	Guy Frederick Marrian Dept. Physiology and Biochemistry, University College London	Crystalline material from pregnant mare urine provided by BRITISH DRUG HOUSES
1929 Estrone	Edward Albert Doisy Dept. Biological Chemistry, St. Louis	
1929 Estrone	Adolf Butenandt Chemistry Laboratory, University of Gottingen	Raw extracts and crystals from pregnant mare urine provided by SCHERING
1929 Estrone	Ernst Laqueur Pharmacotherapeutic Laboratory, Amsterdam	Benzene extracts from pregnant mare urine provided by ORGANON
1931 Androsterone	Adolf Butenandt Chemistry Laboratory, University of Gottingen	Extracted from 15 000 liters of urine provided by the Prussian Police Academy in Berlin and processed by SCHERING
1935 Testosterone	Ernst Laqueur Pharmacotherapeutic Laboratory, Amsterdam	Isolated from bull testes Provided by ORGANON

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policemen from Berlin, which was then processed by Schering to obtain 15 mg of this first androgen (Butenandt 1931). In 1935 Ernst Laqueur (1866–1947) and his group in Amsterdam extracted and isolated 10 mg testosterone (androsten-17α-ol-3-one) from 100 kg of bull testes, which they found more active than androsterone, and named it "testosterone" (David *et al.* 1935). In the same year Butenandt and Hanisch (1935) as well as Ruzicka and Wettstein (1935) published the chemical synthesis of testosterone. This marked the beginning of modern clinical pharmacology and endocrinology of testosterone, and male reproductive physiology.

Soon after its synthesis testosterone became clinically available, first in the form of pellets (Deansley and Parkes 1937; Parkes 1965) and then as injectable esters, that is, testosterone propionate, with a short half-life. And, from the mid-1950s on, the longer-acting testosterone enanthate (Junkmann 1952; 1957) appeared, which remained the major testosterone preparation for half a century. Also in 1935, 17α-methyltestosterone was synthesized and its oral effectiveness was demonstrated (Ruzicka *et al.* 1935). However, due to its 17α-structure it turned out to be liver toxic (Werner *et al.*1950; Nieschlag 1981), a fact which gave testosterone in general a bad name among physicians, as this toxicity was also suspected for testosterone without reason; eventually in the 1980s this androgen became obsolete for clinical use in Europe. In the late 1970s the orally effective testosterone undecanoate, absorbed from the gut via the lymph to avoid the first-pass effect in the liver, was added to the spectrum of testosterone preparations used clinically (Coert *et al.* 1975; Nieschlag *et al.* 1975) (see also Chapter 15).

In the 1950s and 1960s the pharmaceutical industry became more interested in new androgens than in testosterone itself, and concentrated its androgen research on the chemical modification of steroid molecules in order to disentangle the various effects of testosterone and produce predominantly erythropoietic or anabolic steroids (Kopera 1985). In 1956 contemporary textbooks on androgens had already described 256 androgenic steroids (Dorfman and Shipley 1956), and by 1976 the number had increased to more than 1000 (Kochakian 1976).

However, it proved impossible to produce androgens with only *one* effect out of the spectrum of testosterone activities; at best, one of these effects could be emphasized, but the other effects remained. The steroid with pure anabolic effects on muscles or bones to treat cachexia, osteoporosis or small stature, or pure erythropoietic effect for the treatment of anemia without androgenization could not be found. Nevertheless, anabolic and similar steroids were clinically used, but disappeared again in the wake of evidence-based medicine (Kopera 1985). However, they continued their existence for illegal use and abuse for doping in sports and bodybuilding (see Chapters 24 and 25). Regrettably, at that time the pharmaceutical industry neglected the chance to develop testosterone preparations better suited for the substitution of hypogonadal patients than the existing testosterone esters. It remains to be seen whether the current search for selective androgen receptor modulators (SARMs) will take a more rewarding course than did anabolic steroids (see Chapter 21).

From the 1970s the newly developed testosterone immunoassays (see Chapter 4) made serial testosterone determinations in blood possible and, when applied to pharmacokinetic studies, it turned out that all available testosterone preparations resulted in unphysiologically high or low serum levels which were undesirable in substitution therapy. Clinicians assembled at a workshop on androgen therapy sponsored by the WHO, and US National Institutes of health (NIH) and Food and Drug Administration (FDA) in 1990 came to the conclusion: "The consensus view was that the major goal of therapy is to replace testosterone levels at as close to physiologic concentrations as is possible" (World Health Organization 1992), and demanded that new testosterone preparations better suited for clinical use be manufactured.

In the mid-1990s, transdermal testosterone patches applied to the scrotal skin became the first transdermal testosterone preparation in clinical use (Bals-Pratsch *et al.* 1986). They had been invented by Virgil Place at ALZA in Palo Alto, a company specializing in new forms of delivery of known drugs (Atkinson *et al.* 1998). However, although clinical results with this preparation were excellent, and for the first time physiological serum levels could be achieved under testosterone substitution, physicians were reluctant to prescribe a medication to be applied to the scrotum and preferred a subsequently developed non-scrotal system (Meikle *et al.* 1992). This, however, caused unpleasant skin reactions as it required an enhancer to drive testosterone through the skin. For this reason the advent of the first transdermal testosterone gel was welcome. This gel became

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available in 2000 for the treatment of male hypogonadism, first in the USA and later also in other countries (Wang *et al.* 2000). Finally in 2004 the intramuscular testosterone undecanoate preparation entered the market and soon achieved great popularity as a real testosterone depot preparation (see Chapter 15).

Testosterone undecanoate had originally been used in oral capsules (see above), but had been turned into an injectable preparation by Chinese investigators using tea seed oil as a vehicle (Wang *et al.* 1991). When the author came across it at an exhibition accompanying an andrology symposium in Beijing in 1993, samples were brought to Germany, injected into monkeys and showed a surprisingly long half-life. A long half-life was confirmed in volunteering hypogonadal men who all showed serum levels in the normal range (Behre *et al.* 1999). When finally a company was interested in this fascinating preparation, it was "Europeanized" by using castor oil as vehicle and was developed as Nebido® for clinical use (Nieschlag 2006).

1.4.3 Early descriptions of syndromes of hypogonadism

It may not have been a coincidence, but rather a sign of heightened interest in the hypogonadism clinics, that at the same time as testosterone became available for clinical use (i.e. when rational treatment became possible), the major syndromes of primary and secondary hypogonadism were first described: that is, the Klinefelter syndrome (Klinefelter *et al.* 1942) and the Kallmann syndrome (Kallmann *et al.* 1944). Pasqualini and Bur (1950) described the first case of the fertile-eunuch syndrome, characterized by all symptoms of lack of testosterone, but active spermatogenesis; Del Castillo *et al.* (1947) published the first five cases suffering from Sertoli-cell-only syndrome. Also at that time the symptoms of the aging male were first described systematically, but unfortunately wrongly termed as "male climacteric" (Werner 1945), starting a controversial discussion that continues until today (see Chapter 16). E. C. Reifenstein (1947) first described a syndrome with partial androgen insensitivity (PAIS) that carries his name to date, and J. M. Morris (1953) published the first cases of complete androgen insensitivity (CAIS) as "testicular feminization in male pseudo-hermaphroditism" – of course without knowing anything about the androgen receptor or androgen receptor mutations (see Chapter 3).

At the same time, Huggins also posted his warning about testosterone influencing prostate carcinoma (Huggins and Hodges 1941), which led to castration (euphemistically called "orchidectomy") as the major treatment of prostate carcinoma, and prevailed until quite recently when androgen deprivation therapy (ADT) by gonadotropin-releasing hormone (GnRH) analogs or antiandrogens was introduced instead or in addition to castration (maximal androgen blockade = MAB). Huggins' statement, "Cancer of the prostate is activated by androgen injections" induced a general fear of testosterone, especially among urologists, that prevented testosterone treatment in many patients who might have needed it. Only recently it became clear that neither endogenous serum testosterone levels (Endogenous Hormones and Prostate Cancer Collaborative Group 2008) nor testosterone treatment (Raynaud 2006) have an impact on prostate carcinogenesis, and now testosterone treatment under careful supervision is even considered for patients after radical prostatectomy suffering from testosterone deficiency (Morgenthaler 2007). However, orchidectomy will continue in the foreseeable future to remain the major option for treatment of prostate carcinoma (Damber and Aus 2008). Thus, castration continues to be recommended for therapeutic purposes as it had already been promulgated during Greco-Roman times and the Middle Ages for the treatment of leprosy, epilepsy, gout, priapism, excessive masturbation and insanity (Melicow 1977), reflecting the knowledge or rather the lack of knowledge of the respective period. There remains the hope that research will eventually result in more humane and patient-friendly methods of treatment as we have witnessed the transition from castration to ADT for treating sexual offenders (Gooren 2011).

1.5 Key messages

- The importance of the testes for normal male function and reproduction has been known since antiquity.
- Correspondingly, castration has also been practiced since antiquity to produce obedient slaves, harem custodians, civil servants and soldiers, as well as for punishment and revenge.

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